Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

Central Research

April 19, 1999

Department of Clinical Research

Via Facsimile
Center for Drug Evaluation and Research
Food and Drug Administration
5630 Fishers Lane, Room 1061
Dockets Management Branch (HFA-305)
Rockville, MD 20852

RE: Docket 99D-0121; Draft Guidance for Industry on Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System

Dear Sir or Madam:

Please refer to the Federal Register Notice Volume 64, page 7897 published on 2/17/99 announcing the availability of the Draft guidance document, "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System" for comment. Pfizer appreciates the opportunity to provide comments on evolving Agency policy and views the comment process for guidance as an important collaboration between the Agency and the regulated industry. We commend the Agency on the development of the guidance to build upon the Agency's vast experience in bioequivalency analysis in both the New Drug and Generic Drug arenas.

While we agree that there are many instances where it is appropriate to waive bioequivalence studies, we urge the Agency to be cautious of when one has sufficient underlying knowledge of the dosage form and the entity itself to be able to judge when to waive bioequivalency. Typically, when a new entity is developed, its bioavailability is extensively characterized. This knowledge base along with the accompanying chemical and physical characterization of the new entity and its dosage forms allows one to make good judgements of when it may not be necessary to perform bioavailability or bioequivalency studies. In the absence of such a background development history it may not be feasible to appropriately judge when there may be subtle characteristics that may afford a non-bioequivalent drug product.

Conversely, there may be instances when one's extensive development background allows judgements that there are situations beyond those described in this guideline where it might be appropriate to waive bioequivalency. It would be appropriate in these instances

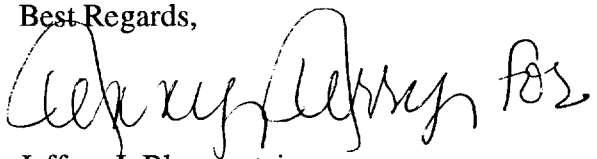
to discuss these opportunities with the Agency on a case-by-case basis. This may include examples that do not fit formally the requirements listed under section V (e.g., an excipient is GRAS but may not be listed as being used in a previously approved IR dosage form).

We request the Agency clarify an apparent contradiction regarding the need to perform BA studies on the pivotal trial dosage form. In section VII.A it is suggested that this study may be waived. However in section VII.A.2 it is recommended that in fact a BA study be performed on the pivotal trial formulation. If the entity fits the chemical and physical characteristics to allow a waiver under this guideline, then regardless of whether a formulation is in early clinical studies or a pivotal study it is anticipated that the dosage form itself is not important to bioavailability. The bioavailability characterization of the pivotal clinical trial formulation serves little purpose but to set a future basis to provide waivers to future formulations, specifically those that are the subject of ANDAs. Therefore, if one accepts the premise of the waiver concept described in this guideline, then the additional bioavailability characterization in the pivotal study is an unnecessary added burden for the original drug developer.

Regarding the permeability characterization with in vitro models described in the guidance, we feel that correlation to an in vivo system with 20 model compounds is excessive. One would expect that ten compounds are sufficient to validate the system. In addition when characterizing the model, the guidance proposes that the compound should demonstrate stability over 3 hours at 37°C. Depending upon the test conditions, alternative approaches such as demonstrating stability at room temperature for 24hours maybe sufficient. Pfizer feels that while the guideline proposes only that some transporters in the in vitro models need be characterized, it is necessary to characterize all known transporters that may be involved in the transport of the drug. In addition, the guideline proposes that two controls be run during each study. Additional controls, specifically those that are substrates for the different transport mechanisms, should be run to confirm activity during the assay.

We again thank the Agency for the opportunity to provide these comments and would welcome an opportunity to discuss them in more detail should this be helpful as the deliberations on this topic continues.

Best Regards,



Jeffrey J. Blumenstein
Director, Regulatory Chemistry, Manufacturing and Controls Operations
(860) 441-0429

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